201-14450A

HIGH PRODUCTION VOLUME (HPV) CHALLENGE PROGRAM

TEST PLAN

FOR

HYDROQUINONE bis(2-HYDROXYETHYL)ETHER

CAS NO. – 104-38-1

PREPARED BY:

ARCH CHEMICALS, INC.

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TABLE OF CONTENTS

OVERVIEW

Arch Chemicals, Inc. (Arch) hereby submits for review and public comment the test plan for hydroquinone bis(2-hydroxyethyl)ether (HQEE; CAS # 104-38-1) under the Environmental Protection Agency's High Production Volume Chemical Challenge Program. It is the intent of Arch to use existing data, data from a structurally similar compound and estimated values using predictive computer models acceptable to EPA to adequately fulfill the Screening Information Data Set (SIDS) for the physical/chemical endpoints, environmental fate, ecotoxicity and human health-related toxicology.

HQEE is produced using hydroquinone and ethylene oxide and is used for polyurethane reactions as a chain extender. Chain extenders are low molecular weight substances that are capable of reacting with isocyanate groups to produce polyurethanes. HQEE has attained commercial significance for cast polyurethane elastomers as well as in thermoplastic elastomers to produce polyurethanes. These polyurethanes are very resistant to mechanical abrasion. The reaction using HQEE to produce polyurethanes is performed under temperature-controlled conditions in a polyurethane mixing and metering unit. This unit feeds components into the mixing head where the reaction between the isocyanate and HQEE begins. The reaction is completed in a closed mold to prevent reaction with atmospheric moisture. This unit is a sealed system because any exposure to moisture would compromise the reaction between HQEE and the isocyanate. The nature of this operation allows for very tight control of the HQEE; thus employee exposure to this material is low.

This chemical is not sold to the individual consumer. Its uses are in the industrial workplace where exposures are tightly controlled.

TEST PLAN SUMMARY

Hydroquinone bis(2-hydroxyethyl)ether CAS # 104-38-1	Information	OECD Study	Other	Estimation	GLP	Acceptable	New Testing Required
STUDY	Y/N	Y/N	Y/N	Y/N	Y/N	Y/N	Y/N
PHYSICAL-CHEMICAL DATA							
Melting Point	Y	-	-	Y	N	Y	N
Boiling Point	Y	-	-	Y	N	Y	N
Vapor Pressure	Y	-	-	Y	N	Y	N
Partition Coefficient	Y	-	-	Y	N	Y	N
Water Solubility	Y	-	-	Y	N	Y	N
ENVIRONMENTAL FATE DATA							
Photodegradation	Y	-	-	Y	N	Y	N
Stability in Water	Y	Y	-	-	Y	Y	N
Biodegradation	Y	N	-	N	N	Y	N
Transport between Environmental Compartments (Fugacity)	Y	-	-	Y	N	Y	N
ECOTOXICOLOGICAL DATA							
Acute Toxicity to Fish	Y	Y	-	-	Y	Y	N
Acute Toxicity to Aquatic Invertebrates	Y	Y	-	-	Y	Y	N
Toxicity to Aquatic Plants	Y	-	-	Y	N	Y	N
MAMMALIAN TOXICOLOGICAL DATA							
Acute Toxicity	Y	N	-	-	Y	Y	N
Genetic Toxicity							
Mutation	Y	-	Y	-	N	Y	N
Chromosome Aberration	Y	-	Y	-	N	Y	N
Repeated Dose Toxicity	Y	Y	-	-	Y	Y	N
Toxicity to Reproduction	Y	-	Y	-	Y	Y	N
Developmental Toxicity	Y	-	Y	-	Y	Y	N

TEST PLAN DESCRIPTION FOR EACH SIDS ENDPOINT

A. Physical/Chemical Endpoints

Melting Point – A value for this endpoint was obtained using a computer estimation model (EPIWIN, Version 3.10.).

Boiling Point – A value for this endpoint was obtained using a computer estimation model (EPIWIN, Version 3.10.).

Vapor Pressure – A value for this endpoint was obtained using a computer estimation model (EPIWIN, Version 3.10.).

Partition Coefficient – A value for this endpoint was obtained using a computer estimation model (EPIWIN, Version 3.10.).

Water Solubility – A value for this endpoint was obtained using a computer estimation model (EPIWIN, Version 3.10.).

Conclusion – All endpoints have been satisfied by the utilization of data obtained from the various physical/chemical data modeling programs. The results from the utilization of these computer modeling programs are recognized by EPA as acceptable in lieu of actual data or values obtained from literature references. Thus, no new testing is needed in the area of physical/chemical properties.

B. Environmental Fate Endpoints

Photodegradation – A value for this endpoint was obtained using a computer estimation model (EPIWIN, Version 3.10.).

Stability in Water – This endpoint has been satisfied by a study that was conducted according to OECD guidelines (OECD guideline number 111) and GLP assurances.

Biodegradation – This endpoint was satisfied by data generated according to the Zahn-Wellens/EMPA test for inherent biodegradability (OECD guideline number 302B). This testing was conducted according to GLP assurances.

Fugacity – A value for this endpoint was obtained using the EPIWIN Level III portioning computer estimation model (EPIWIN, Version 3.10.).

Conclusion – All endpoints have been satisfied using actual data or through the use of EPA-acceptable estimation models.

C. Ecotoxicity Endpoints

Acute Toxicity to Fish – This endpoint was satisfied by data generated in a 96-hour bioassay using the fathead minnow. The concentrations of the test material were analytically measured at the start and end of the study. The study was conducted under OECD guidelines (OECD guideline number 203) and according to GLP assurances.

Acute Toxicity to Aquatic Invertebrates – This endpoint was satisfied by data generated in a 48-hour bioassay using the species, *Daphnia magna*. The concentrations of the test material were analytically measured at the start and end of the study. The study was conducted under OECD guidelines (OECD guideline number 202) and according to GLP assurances.

Toxicity to Aquatic Plants – A value for this endpoint was obtained using a computer program for estimating the ecotoxicity of industrial chemicals based on structure-activity relationships (Nabholz et al, 2001).

Conclusion – All endpoints have been satisfied using actual data or through the use of EPA-acceptable estimation models. No additional testing is needed in the area of ecotoxicity.

D. Mammalian Toxicological Endpoints

Acute Toxicity – This endpoint was satisfied by data generated via two routes of exposure, oral gavage and dermal application. One study per exposure route was performed and each was conducted as a limit test. Both studies were conducted according to currently accepted scientific methodology and GLP assurances.

Repeat Dose Toxicity – This endpoint was satisfied using data generated in a 28-day study via the oral (feed incorporation) route of exposure. The study was conducted according to OECD guidelines (TG-407) and GLP assurances.

Genetic and Reproductive/Developmental Toxicity – Data do not exist for these endpoints. However, the genetic toxicity (mutation or chromosome aberration) and reproductive/developmental toxicity of HQEE may be predicted from data generated on a structurally similar analog, hydroquinone monomethyl ether (HQMME, CASRN 150-76-5) (Florin et al., 1980; Bartsch et al., 1980; USFDA, 1997). The justification for using HQMME as an analog to satisfy the requirement for data for these endpoints for HQEE is based on the following comparisons for which information or data exist either from studies or from EPA-acceptable computer estimation models for both compounds:

- Molecular weight

    The molecular weight of HQMME is 124. That of HQEE is 198.

- Molecular structure

  A key factor supporting acceptability for use of an analog to predict toxicity is structural similarity. HQMME and HQEE are alkylether-substituted hydroquinones. The former compound is a mono-substituted methylether derivative while the latter compound is a di-substituted hydroxyethylether derivative. Thus, the functional groups attached to the aromatic ring are hydroxy, low molecular weight alkoxy, or low molecular weight hydroxyalkoxy groups.

- Log octanol/water partition coefficient

  This value for HQMME is 1.34 (Camilleri et al., 1988). The value for HQEE is 0.61 (KOWWIN v.1.66).

- Water solubility

  The water solubility of HQMME is 40 g/l (Chemicals Inspection and Testing Institute, 1992). The water solubility of HQEE is 13.4 g/l (WSKOW v1.40).

- Biodegradation

  HQMME and HQEE are inherently biodegradable under aerobic conditions. After 28 days contact time, there was greater than 95% degradation of each compound (Chemicals Inspection and Testing Institute, 1992 (HQMME); Lawrence and Ruffing, 1995 (HQEE)).

- Acute toxicity to fish

  The 96-hour LC_{50} to fathead minnow (*Pimephales promelas*) for HQMME (Geiger et al., 1985) and HQEE (Lawrence and Hirsch, 1995) is 110 mg/l and >1043.7 mg/l, respectively.

- Acute toxicity to aquatic invertebrates

  The 48-hour EC_{50} (immobilization) to *Daphnia magna* for HQMME (Bringman and Kuehn, 1982) and HQEE (Lawrence and Hirsch, 1995) is 7.2-19.3 mg/l and >100.2 mg/l, respectively.

- Acute toxicity to mammals from oral exposure

  The oral LD_{50} (rats, intubation) of HQMME is estimated to be 1630 mg/kg (Hodge, 1949). That for HQEE is >5000 mg/kg (Shepard, 1989).

- Repeated dose toxicity (28-day exposure) to mammals

  HQMME (Hodge, 1949) and HQEE (Hosenfeld and Hankinson, 1988) were administered to rats daily in the diet for 7 and 4 weeks, respectively. HQMME was administered at concentrations of 0.02, 0.1, 0.5, 2.0 or 5.0 %. HQEE was administered at concentrations of 0.1, 0.3 or 1.0 %. No mortality was produced by either compound.

HQMME produced growth depression at dietary concentrations ≥ 0.5 %. Urinary glucose was elevated at ≥ 0.5 %. All hematological variables were comparable to control values at all concentrations. In animals fed ≥ 0.5 % organ weights were decreased, but organ to body weight ratios were comparable to controls. No histopathological change was observed to the heart, lungs, spleen, liver, kidneys, brain, testes and gastrointestinal tract that was compound related. The no-observed-adverse-effect level (NOAEL) in this study was 0.1 % in the diet, which corresponds to a dose of at least 100 mg/kg.

Following HQEE exposure no treatment-related clinical signs of toxicity were observed. There were no statistical body weight differences between any of the treated animals and control animals. The mean blood platelet count for the high-dose males was slightly less than for the control group. No other abnormalities in hematology were noted in the males. No hematological abnormalities were observed in any of the female animals. The clinical chemistry findings in all treated animals were comparable to controls. Relative kidney weights in low- and mid-dose females were lower (p=0.02), but not different from controls in the high-dose females. Absolute kidney weights for all treated female animals were similar to controls. No other organ weight differences were seen in any dose group for either sex. No compound related histopathological change was observed in any organs. The NOAEL in this study was 0.3 % in the diet (249 mg/kg) for male rats and 1.0 % (851 mg/kg) for females.

A review of the physical and toxicological data common to HQEE and HQMME was conducted. Both compounds may be predicted to have a low potential to accumulate in the body as indicated by the octanol/water partition coefficient and water solubility. In fact, HQMME was excreted mainly as conjugates of glucuronic and sulfuric acids and a very small amount was demethylated to give hydroquinone. The acid conjugates accounted for greater than 80 % of the metabolic profile and were excreted rapidly (Cosmetic Ingredient Review, 1985). HQEE would be expected to undergo metabolism to the carboxylic acid derivative and to be excreted rapidly. HQEE and HQMME would not bioaccumulate. Both compounds are readily biodegradable and would not accumulate in the environment. Data from aquatic and mammalian toxicity studies indicate that HQMME is generally more toxic than HQEE. Although HQMME is the more toxic quantitatively, there are no meaningful toxicological differences in the qualitative effects produced by these two compounds for the common endpoints for which data exist.

It is scientifically reasonable to predict that the toxicity of HQEE for genetic and reproductive/developmental toxicity would probably be less than but at least equal to the toxicity of HQMME. Therefore, the use of HQMME as an analog to predict the toxicity of HQEE for the endpoints of genetic and reproductive/developmental toxicity is appropriate.

Conclusion – The endpoints for acute toxicity and repeated dose toxicity have been satisfied with data from studies that were conducted utilizing methods that are scientifically current or according to an established guideline. The endpoints for genetic toxicology and reproductive/developmental toxicology have been satisfied using data from a structurally similar analog, HQMME. No additional testing is needed in the area of mammalian toxicity. Additional testing in the areas of genetic and reproductive/developmental toxicity would not yield any significant information and would result in needless use of animals, which is clearly against EPA policy.

SIDS DATA SUMMARY

Data to assess the various physicochemical properties (melting point, boiling point, vapor pressure, partition coefficient and water solubility) for HQEE were obtained from EPA-acceptable computer estimation modeling programs found in EPIWIN. These data indicate that HQEE is a solid at room temperature with a low vapor pressure. It has a low estimated octanol to water partition coefficient and is moderately soluble in water. The use of these modeled data meet the requirements of the various endpoints and thus there is no need for any additional testing to determine physicochemical properties.

Data to address endpoints for environmental fate of photodegradation, biodegradation and fugacity were obtained from actual studies or EPA-acceptable computer estimation modeling programs found in EPIWIN. As a result of its solubility in water and relatively low volatility, fugacity estimations predict that HQEE will distribute primarily to soil and water. Computer modeling predicts that HQEE would be expected to rapidly degrade in the atmosphere. Results from a biodegradation study indicate that HQEE undergoes rapid biodegradation and would not be expected to be persistent in the environment. The endpoint to determine acid/base-catalyzed hydrolysis has not been satisfied. Data for this endpoint will be based on OECD guideline number 111.

The data for aquatic toxicity endpoints were obtained from actual studies or EPA-acceptable computer estimation modeling programs found in ECOSAR (Nabholz et al., 2001). HQEE is of low toxicity to fish, daphnids and algae. The LC_{50} to fish (96 hours) is >1044 mg/l and the EC_{50} (immobility) to *Daphnia* (48 hours) is >100 mg/l. The EC_{50} (96 hours) to algae is 1672 mg/l.

The data to determine acute toxicity and repeated dose toxicity are from studies that were conducted according to acceptable scientific methodology (acute toxicity) or an OECD test guideline (TG-407). The oral LD_{50} and dermal LD_{50} are greater than 5 g/kg and 2 g/kg, respectively.

HQEE was administered to rats in the diet at concentrations of 0.1, 0.3 or 1.0 % for 28 days. Following exposure no treatment-related clinical signs of toxicity were observed. There were no statistical body weight differences between any of the treated animals and control animals. The mean blood platelet count for the high-dose males was slightly less than for the control group. No other abnormalities in hematology were noted in the males. No hematological abnormalities were observed in any of the female animals. The clinical chemistry findings in all treated animals were comparable to controls. Relative kidney weights in low- and mid-dose females were lower (p=0.02), but not different from controls in the high-dose females. Absolute kidney weights for all treated female animals were similar to controls. No other organ weight differences were seen in any dose group for either sex. No compound related histopathological change was observed in any organs. The NOAEL in this study was 0.3 % in the diet (249 mg/kg) for male rats and 1.0 % (851 mg/kg) for females.

Hydroquinone monomethylether (HQMME) is serving as an analog to predict the genetic toxicity of HQEE. HQMME has been evaluated in two assays for mutagenicity, 1) Ames/*Salmonella* point mutation assay (two studies) and 2) *in vivo* micronucleus assay. HQMME was tested up to 496 μg/plate in *Salmonella* strains TA 98, 100, 1530, 1535 and 1537 with and without metabolic activation. HQMME did not produce mutations in this assay. The potential of HQMME to produce chromosomal aberrations was evaluated in the micronucleus assay using rats. Dermal exposure of HQMME for 6 months failed to induce micronuclei in the test animals. Thus, HQMME was judged to lack the potential to produce chromosomal aberrations.

HQMME is also serving as an analog to predict the reproductive/developmental toxicity of HQEE. Two studies were conducted to determine the potential of HQMME to affect fertility and reproductive performance. Both studies will be included in the robust summary because they are complimentary in the data that was generated from each. In the first study HQMME was administered once daily (6 hours/day) dermally to rats at 20, 40 or 80 mg/kg. Males were dosed for 4 weeks and females for 2 weeks prior to mating. All animals were dosed throughout the cohabitation period for a maximum of 3 weeks. Females were dosed through gestation day 7 and sacrificed on gestation day 15. Males were dosed through the day before the scheduled sacrifice. In males mating and fertility parameters and sperm quality were not affected by treatment. Testicular weights appeared to be decreased in high dose males, but histological examination of the testes revealed no treatment-related changes. In females estrous cycling, mating, fertility and intrauterine parameters were not affected by treatment. Post-implantation loss and mean numbers of viable embryos, corpora lutea and implantation sites were similar in treated and control groups. There were no treatment-related findings on gross necropsy. There was no treatment-related histopathological change to male animals. The parental systemic NOAEL was determined to be 40 mg/kg/day; for reproductive performance it was considered to be greater than 80 mg/kg/day.

In the second study HQMME was administered once daily dermally (6 hours/day) to the back of rats. The material was applied at a rate of 12, 40 or 120 mg/kg to pregnant F_0 animals (gestation day 6-20). Dams were allowed to deliver naturally. At post-natal day 4, litters were culled and the F_1 animals were evaluated for physical and functional development and reproductive performance. F_1 animals were mated and F_2 fetuses were evaluated on gestation day 20. F_0 animals had dose-related irritation that was severe enough to recommend and proceed with sacrifice of dams and offspring during the first week of lactation. In F_1 animals, treatment-related effects were observed only at the maternally toxic high dose. In that group there was increased pup mortality, decreased pup body weight, and an increased incidence of clinical signs. Four high dose F_0 females had total litter loss between lactation days 1 and 5. Reduced F_1 survival was observed in high dose litters after post-natal day 1 and these pups also had reduced body weights. Estrous cycling in F_1 females and reproductive performance in F_1 animals was unaffected by treatment. Gravid uterine weights and F_2 fetuses were also unaffected. On gross necropsy, the only treatment-related finding in the F_0 dams was reddening, thickening and scabbing of skin at treated sites. No treatment-related gross pathological change was noted in the F_1 pups, F_1 adults and the F_2 pups. Based on this study, the maternal, neonatal, and developmental NOAELs were determined to be 40 mg/kg/day.

The developmental toxicity of HQMME was evaluated in rats and rabbits. In rats the test material was applied once daily to the skin of the back for 6 hours/day on days 6-15 of gestation. The dose rate was 20, 40 or 80 mg/kg/day. The dams exhibited no systemic signs of toxicity. The mean body weight in the high dose group was reduced and was significantly different from controls on gestation days 12-16. No significant differences were seen in numbers of viable or dead fetuses, post-implantation loss, pre-implantation loss, and numbers of corpora lutea and implantation sites. No external malformations or variations were observed. There were no treatment-related visceral or skeletal malformations at any dose. The systemic maternal NOAEL was 40 mg/kg/day and the NOAEL for developmental toxicity was greater than 80 mg/kg/day. In a second study rats were exposed to a daily dermal dose of HQMME on gestation days 1-20. No significant differences were observed between treated and control groups with respect to skeletal anomalies, post-implantation mortality, craniocaudal dimensions and weight of embryos, or placental weights. However, HQMME did produce embryo toxicity as demonstrated by an increase in pre-implantation loss. This study did not meet the requirements for reliability because only one dose of HQMME was used and it was reported only in abstract form. It is being included in the robust summary because embryo toxicity was observed.

In rabbits the test material was applied once daily to the skin of the back for 6 hours/day on days 6-18 of gestation. The dose rate was 4, 12 or 40 mg/kg/day. The dams exhibited no systemic signs of toxicity. No significant differences were seen in litter size, early or late resorptions, numbers of viable or dead fetuses, post-implantation loss, pre-implantation loss, number of corpora lutea, implantation sites, fetal body weights and sex ratio. In this study there were no statistically significant differences among treatment groups in fetal malformations; however, the mid and high dose groups did have an increased incidence of skeletal variations. A NOAEL of 4 mg/kg/day for teratogenicity in rabbits was established.

EVALUATION OF DATA FOR QUALITY AND ACCEPTABILITY

The collected data were reviewed for quality and acceptability following the systematic approach described by Klimisch et al. (1997). The codification described by Klimisch specifies four categories of reliability for describing data adequacy. They are:

1. Reliable without restriction: Includes studies or data complying with Good Laboratory Practices (GLP) procedures, or with valid and/or internationally accepted testing guidelines, or in which the test parameters are documented and comparable to these guidelines.

2. Reliable with restrictions: Includes studies or data in which test parameters are documented but vary slightly from testing guidelines.

3. Not reliable: Includes studies or data in which there are interferences, or that use non-relevant organisms or exposure routes, or which were carried out using unacceptable methods, or where documentation is insufficient.

4. Not assignable: Includes studies or data in which insufficient detail is reported to assign a rating, e.g., listed in abstracts or secondary literature.

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